



**IMACS**

International Myositis Assessment & Clinical Studies Group

# Myositis Core Set Measures of Activity, including MMT8, and the Preliminary Definitions of Improvement

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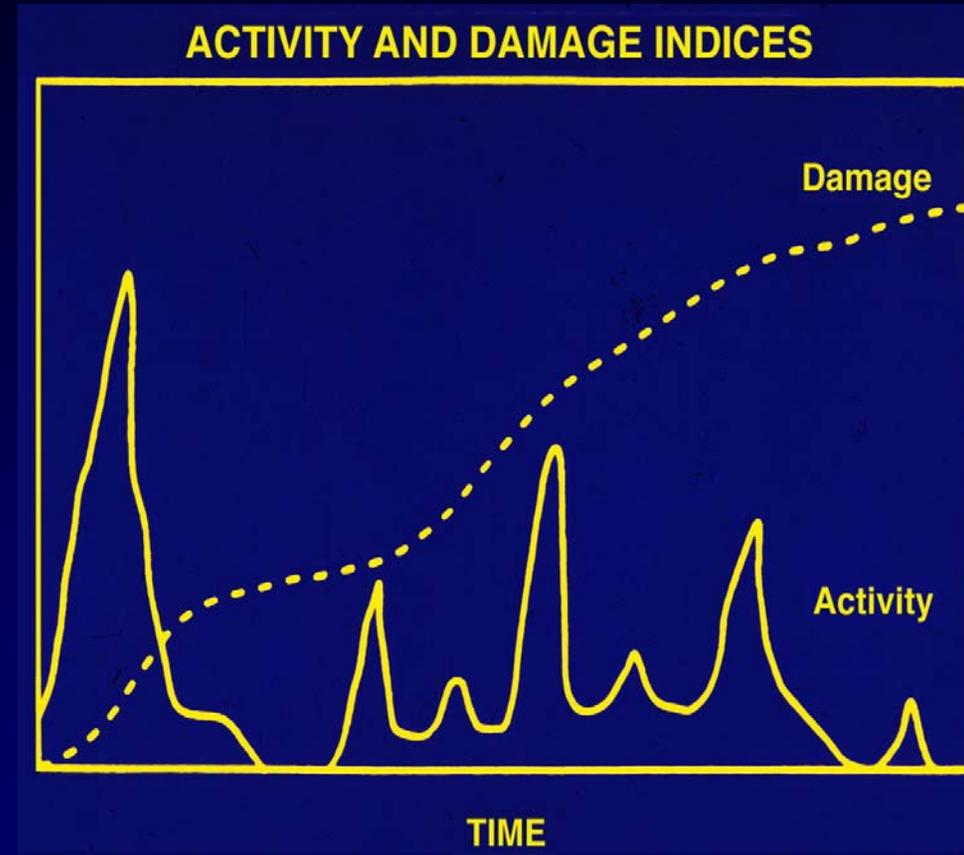
# Disease Activity vs. Damage

- Disease Activity

- Type, extent and severity of reversible manifestations due to myositis
- Excludes other disease processes

- Disease Damage

- Persistent changes in anatomy, physiology, pathology or function resulting from prior active disease, complications of therapy, co-morbid conditions, which do not contribute to an active disease process
- Reflect scarring, atrophy, fibrosis
- Often irreversible and cumulative



# IMACS Core Set Measures

## Disease Activity

- MD Global Activity – VAS/Likert
- Patient/Parent Global Activity – VAS/Likert
- Muscle Strength – MMT:  
0-10 or expanded 0 – 5 using proximal, distal and axial muscles
- Physical Function – [C]HAQ, CMAS
- Laboratory –  $\geq 2$  muscle enzymes
- Extra-Muscular Activity – Myositis Disease Activity Assessment Tool (MyoAct, MITAX)

## Damage – Potential Core Set

- Myositis Damage Index
- MD Global Damage – VAS/Likert
- Physical Function – [C]HAQ

## Patient-Reported Outcomes

- HR-QOL using SF-36/CHQ, PedsQL
- Myositis-specific measure to be developed/validated
- Patient-reported fatigue measures to be developed/validated

# Validation and Performance of Core Set Activity Measures in Adult and Juvenile IIM

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- Good inter-rater reliability
- Good internal reliability
  - Item-total and domain-total correlations moderate to high
  - Moderate level of endorsement for each domain
- Good construct validity
  - High correlation with relevant other measures (i.e., strength and function)
  - Moderate correlation with other core set measures
- Moderate responsiveness
- Good discriminant validity
  - Patients “improved” in a trial showed more change in each core set measure than patients “not improved”

# Manual Muscle Testing in Adult and JIIM

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- Primary outcome measure in 23/24 IIM trials (6 JDM)
- MMT most widely used measure to assess strength in myositis
- Total 24 muscle groups:
  - 2 axial,
  - 7 proximal (bilateral),
  - 4 distal (bilateral);
  - Expanded 0 – 5 MRC scale used for validation studies

<b>5 point</b>	<b>10 Point</b>	<b>Description</b>	
<b>0</b>	<b>0</b>	<b>No contraction of muscle is felt</b>	
<b>1</b>	<b>1</b>	<b>Tendon is visible, but no movement is detected</b>	
<b>2</b>	<b>1</b>	<b>Moves through partial range of motion in the horizontal plane</b>	
<b>2</b>	<b>2</b>	<b>Moves through completion of range of motion in the horizontal plane</b>	
<b>2</b>	<b>3</b>	<b>Moves through completion of range of motion against resistance in the horizontal plane</b>	<b>holds against pressure or moves through partial range of motion in an antigravity position</b>
<b>3</b>	<b>4</b>	<b>Gradual release from test position in an antigravity position</b>	
<b>3</b>	<b>5</b>	<b>Holds test position (no added pressure) in an antigravity position</b>	
<b>3</b>	<b>6</b>	<b>Holds test position against slight pressure in an antigravity position</b>	
<b>4</b>	<b>7</b>	<b>Holds test position against slight to moderate pressure in an antigravity position</b>	
<b>4</b>	<b>8</b>	<b>Holds test position against moderate pressure in an antigravity position</b>	
<b>4</b>	<b>9</b>	<b>Holds test position against moderate to strong pressure in an antigravity position</b>	
<b>5</b>	<b>10</b>	<b>Holds test position against strong pressure in an antigravity position</b>	

# Adult IIM Patients are Weaker than Juvenile IIM

Max Score 120	Adult IIM (n = 114)		Juvenile IIM (n = 99)	
	<u>Baseline</u>	<u>FU</u>	<u>Baseline</u>	<u>FU</u>
<u>%</u>				
25%	81	81	97	106
<b>Median (50%)</b>	<b>90</b>	<b>93</b>	<b>106</b>	<b>111</b>
75%	98	102	112	115
% Patients < 114 (95%)	97%	94%	86%	66%

# Validation and Performance Characteristics of Total MMT

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- In adult and juvenile IIM, demonstrates
  - Excellent internal reliability and consistency
  - Good – excellent inter- and intra-rater reliability (total scores, not individual muscles)
  - Good construct validity; no redundancy with other core set measures
  - Highest correlations with measures of physical function, moderate correlation with global activity, MRI, enzymes

*Hicks et al., Arthritis Rheum., 2000, 43: S194, S195*

# Validation and Performance of Total MMT in Adult and Juvenile IIM

	<u>Adult</u>	<u>Juvenile</u>
Internal consistency (Cronbach's $\alpha$ )	0.93	0.97
Inter-rater reliability (Kendall's W)	NA	0.70
Intra-rater reliability ( $r_s$ )	NA	0.90
Construct validity ( $r_s$ )*	0.31 – 0.63	0.27 – 0.71
Responsiveness (SRM)	0.38	0.55

\*Best correlation with CMAS, HAQ/CHAQ, Steinbrocker Functional Class; correlation with enzymes NS in JIIM

# Total MMT Demonstrates Good Discriminant Validity in Adult IIM Trial Patients\*

<b>Outcome</b>	<b>Median Change</b>	<b>[25%, 75%]</b>	<b>Median Percent Change</b>	<b>[25%, 75%]</b>
<b>Improved (n = 39)</b>	11	[8, 11]	12%	[9, 28%]
<b>No response (n = 46)</b>	0	[-3, 3]	0%	[0, 4%]

\* Number (n) represents number of evaluable trial arms.  
Outcome based on pre-determined criteria for MMT + ADL

# Development of MMT8

- Based on symmetry and patterns of weakness, developed subsets of MMT24 consisting of
  - MMT6: 144 possible subsets of 1 axial, 2 proximal (1 UE, 1 LE), 2 distal (1 UE, 1 LE) muscle groups
  - MMT8: 96 possible subsets of 1 axial, 5 proximal (2 UE, 3 LE), 2 distal (1 UE, 1 LE) muscle groups

for enhanced convenience and efficiency of strength evaluation

- 1 MMT6 and 7 MMT8 subsets met criteria based on internal reliability, internal consistency, responsiveness, intra- and inter-rater reliability, and construct validity
  - Based on performance characteristics in both adult and juvenile IIM
- Nominal group technique used to vote on top subsets among 11 expert clinicians

<b>Subset #</b>	<b>6 or 8 muscles</b>	<b>MMT subscore</b>
<b>5</b>	<b>MMT6</b>	Neck extensors, trapezius, gluteus maximus, iliopsoas, wrist extensors, ankle dorsiflexors
<b>19</b>	<b>MMT8</b>	Neck flexor, trapezius, deltoid, gluteus maximus, iliopsoas, quadriceps, wrist flexors, ankle dorsiflexors
<b>21</b>	<b>MMT8</b>	Neck flexor, deltoid, biceps, gluteus maximus, gluteus medius, quadriceps, wrist flexors, ankle dorsiflexors
<b>22</b>	<b>MMT8</b>	Neck flexor, deltoid, biceps, gluteus maximus, gluteus medius, quads, wrist extensors, ankle dorsiflexors
<b>24</b>	<b>MMT8</b>	Neck extensors, trapezius, deltoid, gluteus maximus, iliopsoas, quadriceps, wrist extensors, ankle dorsiflexors
<b>31</b>	<b>MMT8</b>	Neck extensors, deltoid, biceps, gluteus maximus, iliopsoas, quadriceps, wrist flexors, ankle dorsiflexors
<b>33</b>	<b>MMT8</b>	Neck extensors, deltoid, biceps, glut maximus, iliopsoas, quadriceps, wrist extensors, ankle dorsiflexors
<b>37</b>	<b>MMT8</b>	Neck extensors, deltoid, biceps, glut medius, iliopsoas, quadriceps, wrist extensors, ankle dorsiflexors



# SUBSCORES ARE SENSITIVE TO CHANGE

Standardized Response Mean*			Relative
Subscore	Mean	SE	Efficiency
5	1.05	0.27	0.94
19	1.21	0.26	0.98
21	1.14	0.28	0.91
22	1.25	0.28	1.24
24	1.24	0.26	1.24
31	1.17	0.29	1.03
33	1.25	0.29	1.32
37	1.28	0.27	1.26
* SRM = (visit3–visit1)/std dev (visit3–visit1)			

CONSTRUCT VALIDITY OF ABBREVIATED MMT SUBSCORES								
MEASURE	MMT Subscores							
		5	19	21	22	24	31	
TOTAL MMT SCORES ●		0.95	0.96	0.96	0.96	0.97	0.98	
PROXIMAL MMT SCORES ●		0.81	0.87	0.91	0.91	0.89	0.90	
DISTAL MMT SCORES ●		0.79	0.70	0.65	0.65	0.71	0.70	
MD GLOBAL ACTIVITY ◆		-0.31	-0.39	-0.37	-0.37	-0.34	-0.34	
MD GLOBAL DAMAGE ◆		-0.34	-0.32	-0.32	-0.32	-0.34	-0.39	
ADL (0-90) ●		0.61	0.55	0.57	0.59	0.63	0.62	
PREDNISONE DOSE ■		-0.11	-0.22	-0.20	-0.18	-0.15	-0.18	
STIR +T1 MRI ◆		-0.43	-0.45	-0.45	-0.46	-0.42	-0.44	
ENZYME LEVELS								
CREATINE KINASE ◆		-0.36	-0.43	-0.37	-0.36	-0.37	-0.38	
ALDOLASE ◆		-0.32	-0.40	-0.33	-0.33	-0.33	-0.34	
SGOT ◆		-0.31	-0.42	-0.37	-0.37	-0.34	-0.33	
LDH ◆		-0.40	-0.48	-0.46	-0.45	-0.40	-0.44	
● P<.001	◆ P<.05	■ P<.5						

<b>MMT Subsets</b>	<b>Vote (Rank)</b>	
Neck flexors, deltoid, trapezius, wrist extensors, gluteus maximus, gluteus medius quadriceps, ankle dorsiflexors	<b>18</b>	<b>(1)</b>
Neck flexors, deltoid, trapezius, wrist flexors, gluteus maximus, iliopsoas quadriceps, ankle dorsiflexors	<b>16</b>	<b>(2)</b>
Neck flexors, deltoid, biceps, wrist flexors, gluteus maximus, gluteus medius quadriceps, ankle dorsiflexors	<b>14</b>	<b>(3)</b>
Neck extensors, deltoid, biceps, wrist extensors, gluteus maximus, iliopsoas quadriceps, ankle dorsiflexors	<b>11</b>	<b>(4)</b>

NGT consensus based on face validity, performance characteristics, impact on function, ease of use, positioning of patients with disability.

# MMT-8 for RIM Trial

Muscle Groups	Right (0 – 10)	Left (0 – 10)	Axial (0 – 10)
<b>Axial Muscles (0 – 10)</b>			
Neck Flexors			0-10
<b>Proximal Muscles</b>			
Deltoid	0-10	0-10	
Biceps brachii	0-10	0-10	
Gluteus maximus	0-10	0-10	
Gluteus medius	0-10	0-10	
Quadriceps	0-10	0-10	
<b>Distal Muscles (0 – 40)</b>			
Wrist Extensors	0-10	0-10	
Ankle dorsiflexors	0-10	0-10	
<b>MMT-8 score (0 – 150)</b>	<b>0-70</b>	<b>0-70</b>	

MMT-8 is a set of 8 designated muscles with a potential score = 150

# Adult and Pediatric Specialists Agree on Minimal Important Clinical Change and Rank Importance of Core Set Measures

## IMACS Outcomes Workshop – 2001

<u>Core Set Domain</u>	<u>Median % Change/ Rank</u>	
	<u>Adult</u>	<u>Pediatric</u>
MD Global Activity	20 / 2	20 / 2
Patient/Parent Global Activity	20 / 4	20 / 4
Muscle Strength	15 / 1	18 / 1
Physical Function	15 / 3	15 / 3
Muscle Enzymes	30 / 6	30 / 5
Extra-skeletal Muscle Activity	20 / 5	20 / 5

# First Workshop Summary – Consensus Between Adult and Pediatric Myositis Experts

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- Agreement that strength (MMT) and MD global activity are top measures of improvement
  - Majority of participants require these in a Definition of Improvement (DOI)
- Agreement on the minimum number of measures needed to define improvement (3)
- Agreement in the number of measures allowed to worsen (1 – 2) and degree of worsening (20 – 25%) as part of a DOI

*Rider et al., 2003, J Rheum., 30: 603-17*

# Preliminary Definition of Improvement for IIM Clinical Trials

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Any 3 of 6 core set measures improved  $\geq 20\%$  with no more than 2 (not including MMT) worse by  $\geq 25\%$

*Rider et al. Arthritis Rheum., 2004*

# Preliminary Adult Myositis DOIs Revised to Incorporate Patient Reported Outcomes

<u>Preliminary DOI</u>	<u>Sum (0 – 60)/ Rank</u>	<u>Sensitivity/ Specificity</u>
A1. 3 of any 6 improved $\geq 20\%$ , no more than 2 worse by $\geq 25\%$ , which cannot be MMT	<b>49/ 1</b>	<b>86%/ 88%</b>
A2. MD global improved $> 30\%$ and MMT improved 1 – 15%, OR MMT improved $> 15\%$ and MD global improved $> 10\%$ , no more than 2 worse by $\geq 25\%$	<b>47/ 2</b>	<b>92%/ 89%</b>
A3a. MMT improved $\geq 15\%$ , OR MD global improved $> 30\%$ and MMT improved 1 - 15%, with no more than 2 worse by $\geq 25\%$	<b>23/ 3</b>	<b>88%/ 94%</b>
A3b. 3 of any 6 improved $\geq 20\%$ , no more than 2 worse by $\geq 25\%$	<b>23/ 3</b>	<b>86%/ 88%</b>
A5a. 3 of any 6 improved $\geq 15\%$ , no more than 1 worse by $\geq 25\%$ , which cannot be MMT	<b>19/ 5</b>	<b>94%/ 77%</b>
A5b. MD global improved $> 30\%$ and MMT improved 1 – 15%, OR MMT improved $> 15\%$ and MD global improved $\geq 10\%$	<b>19/ 5</b>	<b>91%/ 92%</b>

# Top Preliminary DOIs for Juvenile Myositis Similar to ACR Pediatric30 for JRA

<u>Preliminary DOI</u>	<u>Sum(0–65)/ Rank</u>	<u>Sensitivity/ Specificity</u>
P1. 3 of any 6 improved $\geq 20\%$ , no more than 2 worse by $\geq 25\%$ , which cannot be MMT	<b>57/ 1</b>	<b>83%/ 98%</b>
P2. 3 of any 6 improved $\geq 20\%$ , no more than 2 worse by $\geq 25\%$	<b>53/ 2</b>	<b>83%/ 98%</b>
P3. 3 of any 6 improved $\geq 20\%$	<b>34/ 3</b>	<b>83%/ 98%</b>
P4. MD global improved $> 30\%$ and MMT improved 1 – 15%, OR MMT improved $> 15\%$ and MD global improved $> 10\%$ , no more than 2 worse by $\geq 25\%$	<b>17/ 4</b>	<b>90%/ 94%</b>
P5. 3 of any 6 improved $\geq 15\%$ , no more than 1 worse by $\geq 25\%$ , which cannot be MMT	<b>15/ 5</b>	<b>94%/ 83%</b>

# Core Set Measures and Preliminary DOIs - Summary

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- Measurement of all 6 core set measures is recommended in all clinical trials
  - Core set measures, including Total MMT and MMT8, have good rater-reliability, internal reliability/consistency, construct validity, responsiveness, and discriminant validity
- Preliminary DOIs have been developed for adult and juvenile myositis, which have clinical face validity and ease of use
  - Top Preliminary DOIs incorporate flexibility in which core set measures improve and limit number of measures able to worsen
  - Preliminary DOIs require prospective validation in clinical trials

# Resources and References

**IMACS Web Site:** <https://dir-apps.niehs.nih.gov/imacs/home.htm>

<https://dir-apps.niehs.nih.gov/imacs/index.cfm?action=home.diseaseactivity>

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